

CLINICAL PHARMACOLOGY BLA REVIEW

Division of Hematology
Office of Blood Review & Research

BLA: 125488

Product: Antivypmin

Indication: Treatment of crotalid viper envenomation

Sponsor: Instituto Bioclon S. A. de C. V.

Date Received: March 18, 2013

Reviewer: Iftekhar Mahmood, Ph. D.

RPM: Edward Thompson

Through: Paul Mintz, M.D.

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INTRODUCTION

Antivipmyn [Antivenin *Crotalinae* (pit viper) Equine Immune F(ab')₂] is intended for the treatment of crotalid envenomation. Clinical consequences of crotalid envenomation include local and systemic effects, both of which may progress for hours to days. Local effects are most common and include pain, edema, ecchymosis, and bullae. Systemic effects include shock, coagulopathy (defibrination with or without thrombocytopenia), myotoxicity, and occasionally, neurotoxicity.

Crotalid viper envenomation in the U.S. is currently treated with one of the two licensed products: CroFab (Protherics, Inc., Brentwood, TN) and Antivenin (Crotalidae) Polyvalent (Wyeth, Marietta, PA). Antivipmyn has been marketed in Mexico for treatment of crotalid envenomation since 1993.

Antivipmyn, (Antivenin, *Crotalinae* (pit-viper) Equine Immune F(ab')₂) is a crotalid antivenom, presented as a lyophilized powder in a 20 mL vial. Antivipmyn contains crotalid antivenom-specific binding fragments, enzymatically derived from equine anticrotalid immunoglobulin. The antibodies are obtained from horses that have been hyperimmunized with

venom of *Bothrops asper* and *Crotalus durissus*. (b) (4)

The product is free from whole IgG and albumin. Each vial of lyophilized white powder contains sufficient antigen binding agent, F(ab)₂ to neutralize no less than 780 times the LD₅₀ of *Bothrops asper* venom and 790 times the LD₅₀ of *Crotalus durissus* venom.

CLINICAL PHARMACOLOGY LABELING COMMENTS

12.1 CLINICAL PHARMACOLOGY

Anavip[®] is composed of venom-specific F(ab')₂ fragments of immunoglobulin G (IgG) that bind and neutralize venom toxins, facilitating redistribution away from target tissues and elimination from the body.^{1,2}

12.3 Clinical Pharmacokinetics

~~A study was designed to evaluate the safety of intravenous Anavip[®] and to characterize its pharmacokinetic profile. Safety was evaluated by collecting signs or symptoms of an adverse reaction after drug administration. Fourteen healthy volunteers received one vial (please mention actual total dose) of intravenous (IV) doses of Anavip[®]. On the first day of Anavip[®] administration, plasma pharmacokinetic blood samples were collected from all subjects at time 0 (prior to drug infusion), 5, 10, 20, 30, 45, 60, 120, and 480 minutes after drug infusion. Additional samples were drawn just prior to discharge (day 1), and on Day 3, Day 5, Day 7, Day 9, Day 11 and Day 21 on days 3, 5, 7, 9, 11, and 21.~~

~~Please remove to clinical section. Safety Results: Reference 5.3.3.1, Clinical Study Report YA 06/07, section 12, page 24~~

~~There were 5 subjects (36%, 5/14) who had adverse events (AEs). In total, there were 10 adverse events; 4 were of mild intensity, and 6 were moderate. None were related to Anavip[®] and all resolved favorably. The most common events were respiratory disorders in 3 subjects. Influenza (2 subjects) was the most common AE. The other events were fever, headache, respiratory tract infection, gastritis, nausea, myalgia, pruritus and urinary tract infection.~~

~~Pharmacokinetic Results: Reference 5.3.3.1, Clinical Study Report YA 06/07, section 11.5.1, page 22~~

~~An open~~ A two-compartment model best fit described the concentration-time data. The pharmacokinetic parameters of Anavip are summarized in Table 2. ~~A summary of pharmacokinetic parameters of concentrations of Anavip[®] (Antivipmyn[®]) in plasma is shown in Table 2.~~

Table 2: Pharmacokinetic parameters of Anavip[®] following a single IV dose to healthy volunteers (n = 13)

Concentrations in Plasma from 13 Normal Volunteers *Reference 5.3.3.1, Clinical Study Report YA-06/07, section 11.5.1, page 22*

	Units	Mean	SD
Area under plasma concentration	AUC _{0-∞} (μg·h/mL)	4144	670
Volume of central compartment	V _c (Liters)	3.5	0.6
Steady-state volume of distribution	V _{ss} (Liters)	6.4	1.7
Mean residence time	MRT (hours)	157	40
Elimination half-life	hours	133	53
Distribution half-life	Alpha HL (h)	16.03	8.98
Total clearance	CL (mL/min)	0.7	0.2
Maximum drug concentration	C _{max} (g/L)	47.84	8.84

RECOMMENDATION/INFORMATION REQUEST

The pharmacokinetic study submitted by the applicant is well designed. However, the applicant has not provided the pharmacokinetic results of the drug following the second dose. The applicant should modify clinical pharmacology labeling as suggested by the FDA.

The following questions will be sent to the applicant and after the receipt of the response the review of this submission will be finalized.

1. Please provide the results of the pharmacokinetic study following the second dose of antivipmyn administered to healthy subjects.
2. Please provide the description of analytical method for the measurement of antivipmyn concentrations used in the pharmacokinetic study.

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Study Title: A Phase I biosafety and pharmacokinetics study of antivipmyn in healthy subjects.

The objectives of this study was to assess the safety, immunogenicity, and pharmacokinetics of intravenous Antivipmyn [antivenin (pit viper) equine immune F(ab')₂] in healthy volunteers.

Fourteen healthy Hispanic subjects were enrolled in this study. There were seven males and seven females in the study (between 19 to 23 years and 54.5 to 83.0 kg body weight). Healthy volunteers received two doses of Antivipmyn, 21 days apart. Subjects received Antivipmyn infusion (one vial = 1.85 mg) administered intravenously over 30 minutes on Day 1 and again on Day 21. The solution was infused through a 20 gauge catheter placed in the subject's antecubital fossa. To prepare the infusion, 5 mL of 0.9% Sodium Chloride for Injection, (b) (4) was aseptically introduced into the vial of Antivipmyn powder to dissolve the powder. The resulting solution was then aseptically withdrawn from the vial and added to 0.9% Sodium Chloride for Injection, (b) (4), in a 100 mL IV bag.

Blood samples for pharmacokinetic study were collected from all subjects at time 0, 5, 10, 20, 30, 45, 60, 120, and 480 minutes after drug infusion. Additional samples were drawn just prior to discharge (day 1), and on days 3, 5, 7, 9, 11, and 21. The last sample (day 21) was drawn prior to administration of the second dose of drug. After the second dose, a sample was also collected on day 21. A 2-compartment model (infusion) was used to describe the concentration-time data for the estimation of pharmacokinetic parameters. The pharmacokinetic parameters are presented in Table 1. Mean concentration-time profile of Antivipmyn is presented in Figure 1.

Table 1: Pharmacokinetic parameters of Antivipmyn following a single intravenous dose to healthy subjects

Parameters	Values
(AUC) _{0-infinity} (microgram*hr/mL)	4144 ± 670
Clearance (mL/minute)	0.7 ± 0.2
Half-life (hrs)	133 ± 53
MRT (hrs)	157 ± 40
Volume of distribution of central compartment (L)	3.5 ± 0.6
Volume of distribution at steady state (L)	6.4 ± 1.7

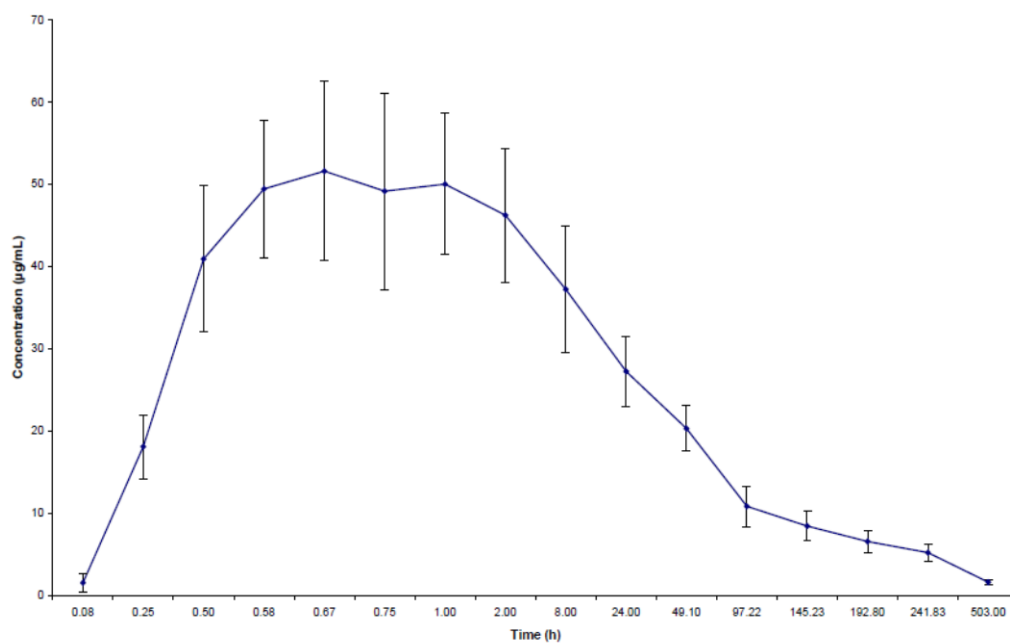
For the assessment of immunogenicity, blood samples were collected at baseline before the first and second Antivipmyn dose, and on day 21 after the second dose of Antivipmyn to test for the development of human anti-horse F(ab')₂ antibodies. The mean concentrations of anti-horse F(ab')₂ antibodies on days 21 and 42 are summarized in Table 2. There was substantial inter-subject variability in the anti-horse F(ab')₂ antibodies concentrations. Human Anti-horse F(ab')₂ antibodies were compared between days 21 and 42 through a non-parametric Wilcoxon sum

rank test for matched samples. Mean values were considered not statistically significant ($p=0.52$).

Table 2: Anti-horse F(ab')₂ antibodies for all subjects

Time	Mean \pm sd (ng/mL)
21 days	705 \pm 1445
42 days	449 \pm 734

Figure 1: Mean concentration-time profile of Antivipmyn



Conclusions: Based on the pharmacokinetics of Antivipmyn, the drug has a low clearance, small volume of distribution, and long half-life. Due to high inter-subject variability in the anti-horse F(ab')₂ antibodies concentrations, it is difficult to draw any conclusion regarding the magnitude of immunogenicity of antivipmyn.